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1. Friedman DJ, et al. Trends and In-Hospital Outcomes Associated with Adoption of the Subcutaneous Implantable Cardioverter Defibrillator in the United States. JAMA Cardiology 2016.

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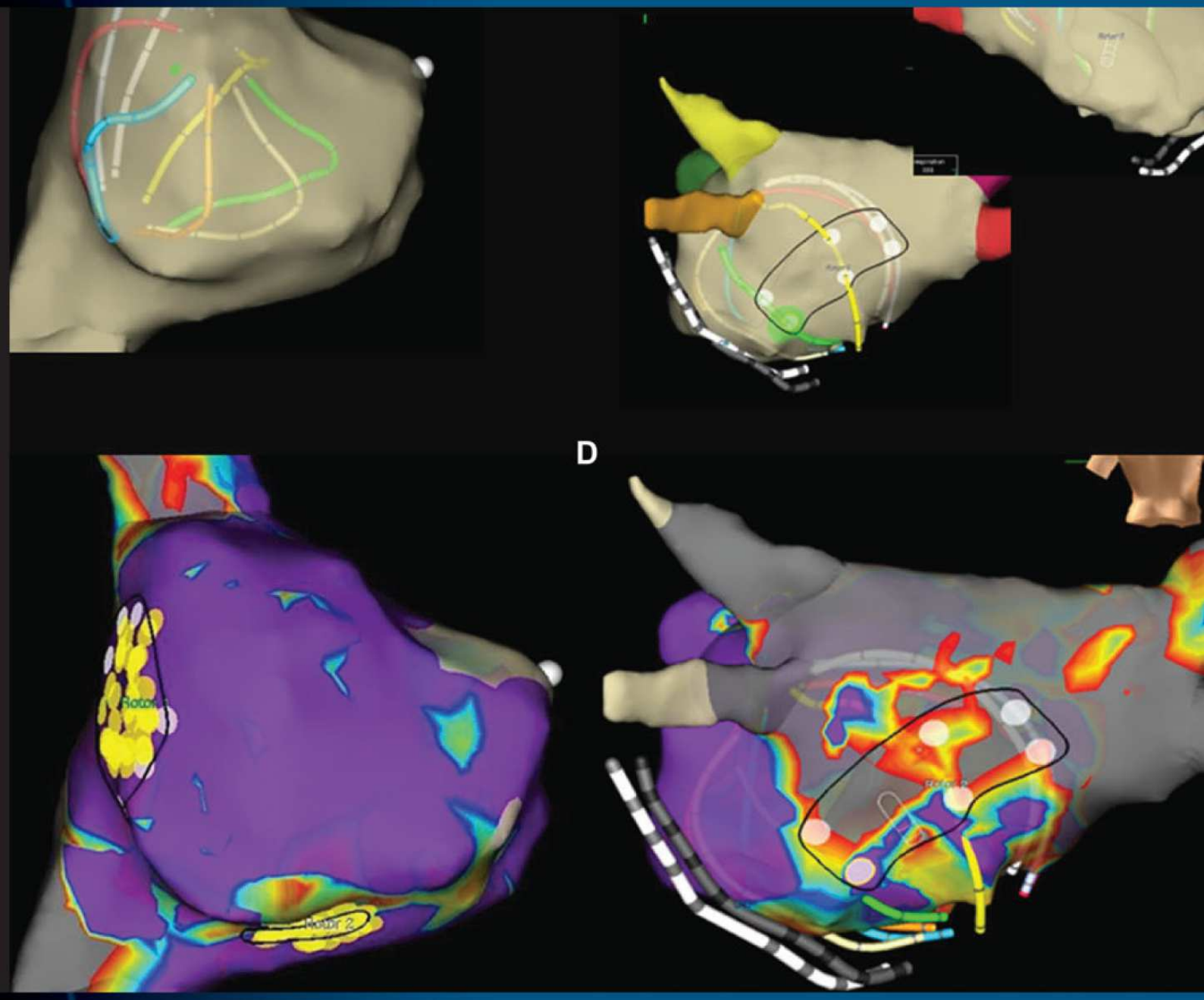

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ORIGINAL ARTICLE

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Fragmented QRS complex as a predictor of exercise-related sudden cardiac death

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Abstract

Introduction: Little is known about the association between electrocardiographic abnormalities and exercise-related sudden cardiac death. Therefore, our aim was to identify possible electrocardiographic findings related to exercise-induced sudden cardiac death.

Methods and results: The FinGesture study includes 3,989 consecutive sudden cardiac deaths in northern Finland between 1998 and 2012, out of whom a total of 647 subjects had a previously recorded electrocardiography acquired from the archives of Oulu University Hospital. In 276 of these cases the death was witnessed, and the activity at the time of death was either rest or physical exercise (PE); in 40 (14%) cases sudden cardiac death was exercise-related and in 236 (86%) cases death took place at rest. Fragmented QRS complex in at least two consecutive leads within anterior leads (V1-V3) was more common in the exercise-group compared to rest-group (17 of 40, 43% vs. 51 of 236, 22%, $P = 0.005$). Pathologic Q wave in anterior leads was more common in the PE group (9 of 40, 23% vs. 26 of 236, 11%; $P = 0.044$). Median QRS duration was prolonged in the exercise-group compared to the rest-group (100 milliseconds vs. 94 milliseconds, $P = 0.047$). QTc interval, the prevalence of inverted T-waves, or other electrocardiographic abnormalities did not differ significantly between the two groups.

Conclusions: As a conclusion, fragmented QRS complex in the anterior leads is associated with an increased risk of sudden cardiac death during PE.

KEYWORDS

electrocardiography, fragmented QRS complex, physical exercise, sudden cardiac death

Sudden cardiac death (SCD) is by definition an unexpected event from a cardiac cause within a certain short time period after the onset of symptoms and is often the first manifestation of the underlying cardiac disease accounting for significant share of years of potential life lost. In the United States, SCD accounts for around 200,000 deaths yearly and in a recent study the age-specific incidence of SCD was 4.2 per 1,000 person-years in the general population.[1,2] A physically active lifestyle hinders the progression of atherosclerosis and reduces the risk of cardiac events and all-cause mortality.[3] However, physical exercise (PE) transiently increases the risk of SCD and this finding is most prominent among the least-fit and during strenuous activity.[3–5] Even if the incidence of exercise-related SCD or sudden cardiac arrest is relatively low in the general population,[6,7] it would be important to identify in advance the subjects with an increased risk for such an event to counsel the subjects or patients individually about the potential risks of strenuous exercise. Research to identify abnormalities in the 12-lead electrocardiogram (ECG) related to SCD has advanced rapidly during the past twenty years. It is hoped that this new information would give rise to tools of risk stratification of SCD. Several ECG abnormalities are linked to an increased risk of SCD, including high resting heart rate, prolonged QRS duration, fragmentation of the QRS complex, malignant forms of early repolarization, prolongation of the QT interval, prolongation of the T-peak to T-end (TpTe) interval, and various T-wave abnormalities.[8–20] In this study, we wanted to investigate if

any of these markers of standard 12-lead ECG are specifically related to exercise-induced SCD in the general population.

1 | MATERIAL AND METHODS

The Finnish study of Genotype and Phenotype Characteristics of Sudden Cardiac Death (FinGesture) included 3,989 consecutive cases of SCD in northern Finland. All cases were autopsy-verified and took place between 1998 and 2012 in northern Ostrobothnia in northern Finland. Practically all unexpected sudden deaths of cardiac origin are included because medico-legal autopsy is mandatory in Finland when the death is sudden and unexpected. The rate of medico-legal autopsy in Finland is the highest in Western countries, and all autopsies were carried out by highly experienced forensic pathologists. The study design is described more precisely in previous studies.[21,22] The information of a possible 12-lead ECG taken incidentally prior to SCD was collected manually from the archives of Oulu University Hospital. The ECGs had previously been recorded for various reasons. The information about the reason for ECG was available in 476 of 647 (74%) subjects. Surgical procedure was the most common reason for ECG (27 %). Acute coronary syndrome (4.2%), syncope (3.2%), and palpitations (2.7%) were less common reasons for ECG. In most cases the ECG had been taken 2 to 5 years prior to the SCD, with a median of 3 years. In this study, we only included deaths from the FinGesture study population that were witnessed and took place within the 1-hour time frame after the onset of symptoms. There were a total of 647 cases of SCD with a previously taken ECG. Police reports, comprehensive death certificates, autopsy reports, and questionnaires to relatives were all used to sort out the physical activity during the time of death. The time frame of physical activity was defined as a 1-hour time frame after the exertion in addition to the period of physical activity itself. The activity during the time of death needed to be at least four metabolic equivalents (four METS) to be considered as PE, which excluded low-intensity household and recreational activity. We assessed the metabolic equivalents of different activities according to the estimates of Jettè et al.[23] The activity was accounted for rest if the person was lying down, sleeping, or sitting when SCD took place. Those whose physical activity at the time of death could not be evaluated accurately or did not meet the criteria of either rest or PE were excluded from the analysis. After exclusions, the primary study population consisted of 276 SCD victims, who were either at rest or engaged in moderate-to-vigorous PE at the time of death and in whom a prior ECG could be gathered.

We also included a control population to compare the prevalence of the addressed ECG abnormalities among exercise-related SCDs to a cohort that represents the middle-aged general population in Finland. The control population consisted of 10,904 subjects either randomly selected or as part of the whole population of a certain area in Finland. This cohort is part of the Social Insurance Institution's Coronary Heart Disease Study (CHD Study) gathered between 1966 to 1972 and includes subjects between ages 30 and 59 years. The study design has been described in more detail earlier.[19,24]

All of the 12-lead ECGs were recorded at rest in a supine position with a paper speed of 50 mm/s and calibration of 1 mV/10 mm. The

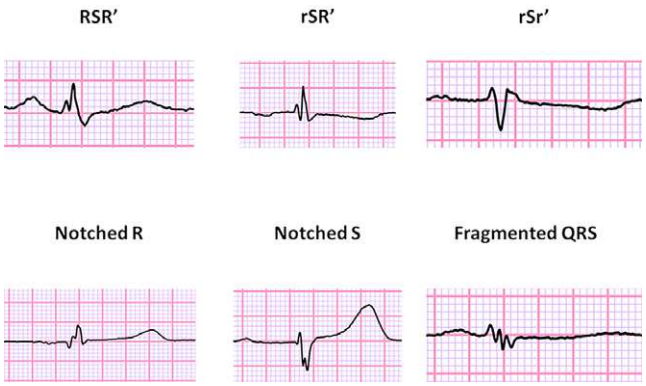

FIGURE 1 Different fragmented QRS morphologies including various RSR' patterns [Color figure can be viewed at wileyonlinelibrary.com]

ECGs of the primary study population were evaluated independently by two researchers. The analysis of ECGs of the control population has been previously described.[14,19,24,25] The ECG criteria of QRS fragmentation was acquired from a previous study,[26] and categorized as lateral (I, aVL, V4-V6), anterior (V1-V3), and inferior (II, III, aVF). Different fragmented QRS morphologies are displayed in Figure 1. All Q waves were divided into pathologic or benign according to their morphology. In leads V2 or V3 any Q wave wider than 20 milliseconds or QS complex were considered as pathologic. In other leads Q waves in two contiguous leads wider than 30 milliseconds and at least 0.1 mV deep or QS complex were considered pathologic. According to these criteria pathologic Q waves were included in the analyses. Left ventricular hypertrophy (LVH) was assessed according to the Sokolow-Lyon criteria. The QT interval was acquired from the lead that had the longest QT interval and was then corrected with heart rate according to the Bazett's formula.

The study complies with the Declaration of Helsinki, and the Regional Ethics Committee of the Northern Ostrobothnia Hospital District approved the study. A permit to collect data from medico-legal autopsies was gained from the National Supervisory Authority for Welfare and Health (Valvira).

1.1 | Statistical analysis

Note that χ^2 analyses were used to detect differences in dichotomous variables. For the continuous variables, Gaussian distribution was assessed by skewness test. In case skewed distribution (|skewness| > 1, QRS duration and QTc interval) was encountered, the variable was transformed into natural logarithm. Distributions were thereafter verified as Gaussian. QRS duration and QTc interval are presented as median (first to third quartile). Otherwise continuous variables are reported as mean (standard deviation). Odds ratios and their 95% confidence interval (CI) were calculated by binary logistic regression. In multivariate regression analysis, fQRS in anterior leads, pathologic Q wave in anterior lead, and prior diagnosed coronary artery disease (CAD) were included in the analysis. Another multivariate analysis was performed with different ECG variables (fQRS in anterior/lateral/inferior leads, Q wave in anterior leads, LVH, QTc, resting

TABLE 1 Subject characteristics in SCD study groups

Variable	PE Group (n = 40)	Rest-Group (n = 236)	P Value
Age (years)	56.5 ± 7.8	55.7 ± 11	0.89
Male gender	39/40 (98%)	181/236 (77%)	0.002
BMI (kg/m^2)	26.4 ± 3.9	28.0 ± 6.8	0.155
Heart rate on previously taken ECG (bpm)	74.9 ± 24.9	81.5 ± 19.2	0.056
Prior diagnosis of cardiac disease	29/39 (74%)	154/235 (66%)	0.28
Prior diagnosis of CAD	18/38 (47%)	60/229 (26%)	0.008
Ischemic heart disease at autopsy	35/40 (88%)	137/236 (58%)	0.00038

Comparisons were made between physical-exercise (PE) versus rest-groups. BMI = body mass index; CAD = coronary artery disease; ECG = electrocardiography; PE = physical exercise; SCD = sudden cardiac death.

TABLE 2 The distribution of ECG abnormalities in PE group versus rest-group

ECG Abnormality	PE Group (n = 40)	Rest Group (n = 236)	P Value
fQRS in anterior leads	17/40 (43%)	51/236 (22%)	0.005
fQRS in inferior leads	20/40 (50%)	109/236 (46%)	0.56
fQRS in lateral leads	12/40 (30%)	66/236 (28%)	0.79
Q wave in anterior leads	9/40 (23%)	26/236 (11%)	0.044
Mean QTc time, median (first to third quartile)	459 (439–490)	474 (443–510)	0.11
QRS duration; lead V5, median (first to third quartile)	100 (89–116)	94 (86–108)	0.047
LBBB	2/40 (5.0%)	18/236 (7.6%)	0.55
RBBB	3/40 (7.5%)	10/236 (4.2%)	0.37
LVH (The Sokolow-Lyon criterion)	4/40 (10%)	17/236 (7.2%)	0.50
Mean T-peak to T-end interval (milliseconds)	113 ± 22	116 ± 24	0.46
Inverted T-wave in anterior leads	0/40 (0%)	22/236 (9.3%)	0.044
Inverted T-wave in lateral leads	10/40 (25%)	60/236 (25%)	0.96
Inverted T-wave in inferior leads	10/40 (25%)	48/236 (20%)	0.50

Comparisons were made between PE and rest-groups. Continuous variables are presented as mean (standard deviation), if the variable was normally distributed. Otherwise continuous variables are presented as median (first to third quartile). ECG = electrocardiography; fQRS = fragmented QRS complex; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; PE = physical exercise; RBBB = right bundle branch block.

heart rate, QRS duration, T-inversion in anterior/lateral/inferior leads, LBBB, RBBB). A P value < 0.05 was considered statistically significant. The Statistical Package for Social Studies 21 (SPSS Inc., Chicago, IL, USA) was used to perform the analyses.

2 | RESULTS

A total of 35 (35 of 276, 13%) deaths took place during PE and five cases (5 of 276, 1.8%) within a 1-hour period after the exertion, creating the PE group (n = 40). The rest-group comprised 236 subjects, who died suddenly at rest. The subject characteristics are presented in Table 1. There were significantly more men in the PE group than in the rest-group. The prevalence of any prior cardiovascular diagnosis was common and statistically uniform in the PE and rest-groups. However, CAD, both previously diagnosed or as an autopsy finding, was more common in the PE group than in the rest-group (18 of 38, 47% vs. 60 of 229, 26%, P = 0.008; 35 of 40, 88% vs. 137 of 236, 58%, P = 0.0004, respectively). The control population consisted of a total of 10,904 subjects. Compared to the PE group, the control population was younger (43 years vs. 57 years, P = 0.001), had a larger proportion of females (47% vs. 2.5%, P < 0.0001), and had less often prior cardiovascular diagnosis (8.2% vs. 74%, P < 0.0001).

The ECG abnormalities and their distribution between the PE group and the rest-group are presented in Table 2. Those with exercise-related SCD had more often fragmented QRS complex (fQRS) in at least two consecutive anterior leads V1-V3 compared to the rest-group. When analysis was restricted to patients with a prior diagnosis of CAD (n = 78), fQRS in the anterior leads was even more commonly found in the exercise-related SCD compared to those with SCD at rest (9 of 18, 50% vs. 12 of 60, 20%, P = 0.012), with an unadjusted odds ratio of 4.0 (95% CI 1.3–12, P = 0.015) (Figure 2). The subjects in the PE group had more often a pathologic Q wave in the anterior leads (9 of 40, 23% vs. 26 of 236, 11%, P = 0.044), but no difference in the prevalence of Q waves in other leads was observed. The median corrected QT time (QTc) was similar in the PE group and rest-group and it was actually a bit longer in the rest-group even though this finding was not statistically significant (Table 2). The PE group had on average a wider QRS complex (100 milliseconds vs. 94 milliseconds, P = 0.047). There were, however, no differences between the

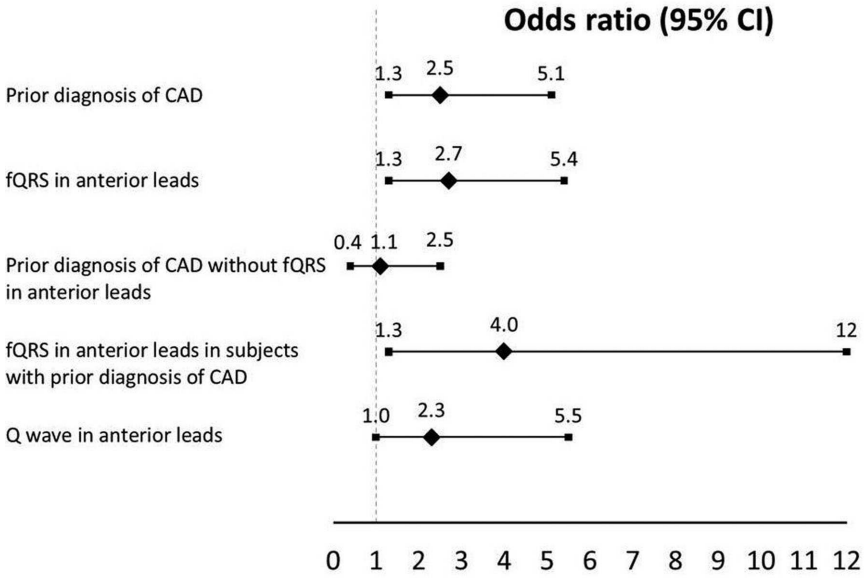

FIGURE 2 Odds ratios calculated for SCD during PE compared to SCD at rest. All presented odds ratios were statistically significant ($P < 0.05$), except for prior diagnosis of CAD without fQRS in anterior leads ($P = 0.82$). CAD = coronary artery disease; fQRS = fragmented QRS complex

TABLE 3 Univariate and multivariate odds ratios for exercise-related SCD

Variable	Univariate OR	Multivariate* OR	P Value for Multivariate Analysis
fQRS in anterior leads	2.7 (1.3–5.4)	2.4 (1.1–5.0)	0.022
Q wave in anterior leads	2.3 (1.0–5.5)	1.9 (0.78–4.9)	0.15
Prior diagnosed CAD	2.5 (1.3–5.1)	2.3 (1.1–4.8)	0.021

*fQRS in anterior leads, Q wave in anterior leads and prior diagnosed CAD were included in the multivariate analysis. CAD = coronary artery disease; fQRS = fragmented QRS complex; OR = odds ratio, SCD = sudden cardiac death.

PE and rest-groups in the prevalence of left or right bundle branch block. In the PE group the prevalence of LVH was 10% (4 of 40), which was similar in the rest-group (7.2%, 17 of 236). The PE group had less often inverted T-waves in the anterior leads compared to the rest-group and this finding was also statistically significant (0 of 40, 0% vs. 22 of 236, 9.3%, $P = 0.044$). No differences could be found in the mean TpTe interval or in T-wave inversions in other than anterior leads.

When the ECG abnormalities were compared between the PE group and the control population, the ECG abnormalities were considerably less common in the control population with the exception of LVH, which was a significantly more common finding in the control population compared to the PE group (31% vs. 10%, $P = 0.004$).

Unadjusted odds ratios of exercise-related SCD compared to SCD at rest for different combinations of prior diagnosed CAD, fQRS in anterior leads, and pathologic Q wave in anterior leads are displayed in Figure 2.

There seemed to be overlap between fQRS in anterior leads, pathologic Q wave in anterior leads, and prior diagnosis of CAD so we included these variables in a multivariate analysis. After these adjustments the individual effect of fQRS in anterior leads remained significant with an odds ratio of 2.4 (1.1–5.0, $P = 0.022$). Adjusted odds ratios are presented in Table 3. We also included the ECG variables (fQRS in anterior/lateral/inferior leads, Q wave in anterior leads, LVH, QTc, resting heart rate, QRS duration, T-inversion anterior/lateral/inferior, LBBB, RBBB) in a multivariate regression analysis and fQRS in anterior leads had an odds ratio of 2.9 (1.3–6.8, $P = 0.013$) for exercise-related SCD. Other variables did not reach statistical significance.

3 | DISCUSSION

Our study shows that fQRS in at least two consecutive anterior leads of a resting 12-lead ECG is significantly more common among those who subsequently died suddenly in relation to exercise compared to those who suffered SCD during rest, or among the general population. fQRS is thought to represent myocardial scarring and fibrosis due to previous ischemia or infiltrative lesions in many different cardiac diseases. PE is thought to lower the threshold for scar-related reentrant ventricular arrhythmias. It has also been speculated that excessive PE may cause myocardial fibrosis, creating a substrate for ventricular arrhythmias.[27] Previous studies have shown that fQRS among patients with CAD is an independent risk factor for cardiac events and mortality.[26,28] In patients with CAD, the absolute number of leads with fQRS, regardless of anatomical location, has been shown to predict cardiac death.[29] There is also evidence of adverse outcome of fQRS in lateral leads even in the general population.[25] In our current study, the prevalence of fQRS in anterior leads was accentuated among

those with a prior diagnosis of CAD and exercise-related SCD. By contrast, subjects with CAD but without fQRS did not have an increased prevalence of exercise-related SCD. Vigorous PE is considered a trigger of ventricular arrhythmias when a substrate, such as myocardial scarring, is present. fQRS in anterior leads might reveal an underlying cardiac abnormality affecting the septal and/or anterior myocardium. This in turn mirrors an increased risk of SCD and in our current sample an increased risk of exercise-related SCD. In our previous study we showed that ischemic heart disease, myocardial scarring and cardiac hypertrophy were autopsy-findings more often related to exercise-related SCD.[30] All these factors might explain the presence of fQRS. Pathologic Q waves in anterior leads were also present more commonly in the PE group. However, this finding could not be expanded to lateral or inferior leads. There is likely overlap between pathologic Q waves and fQRS while both might manifest similar abnormality in the myocardium. When adjusted in a multivariate regression analysis, the effect of fQRS in anterior leads remained significant in contrast to Q waves. We did not find any difference between the PE group and rest-group in the prevalence of fQRS in other than anterior leads. fQRS in inferior or lateral leads mirror different anatomical regions and this difference might alter the effect of PE. fQRS in anterior leads was also the only ECG variable that reached statistical significance in multivariate regression analysis of different ECG variables.

The association between a prolonged QRS duration and the risk of SCD is well-established.[11,31] Left ventricular dysfunction is often associated with QRS complex prolongation and, as such, increases the risk of SCD. However, a prolonged QRS duration could also be a marker of fibrosis or depolarization abnormalities, which may lead to ventricular arrhythmias. In our current study, the median QRS duration was wider among exercise-related SCDs. This finding might reflect a more severe underlying myocardial abnormality, which in turn increases the risk of SCD when a trigger, such as PE, is present.

Other ECG variables, such as mean QTc interval (Bazett's formula), TpTe interval, or presence of T-wave inversions did not differ between the PE and rest-groups but all these variables differed between the PE group and the control population. In the general population prolonged QTc interval is associated with a higher risk of SCD.[16] A meta-analysis conducted a few years ago verified the increased risk of overall mortality and SCD when QTc interval was prolonged.[32] Concurrent with the present findings, TpTe interval has been found to be longer among SCD victims.[18] This finding is thought to be due to transmural dispersion of repolarization leading to ventricular arrhythmias.[33] However, we did not find any difference in mean TpTe interval between exercise-related deaths and deaths that occurred during rest. Several cardiac diseases can also cause T-wave alterations, most notably T-wave inversions. Inverted T-waves in other than right precordial leads have been shown to increase the risk of cardiac mortality and SCD. T-wave inversions in right precordial leads may present an underlying cardiac disease such as hypertrophic cardiomyopathy, myocardial ischemia or ARVC, but have not been linked to an increased risk of SCD in the general population.[19] In our study, none of the subjects in the PE group had T-wave inversions in the anterior leads. The prevalence of T-wave inversions in the anterior leads was similar also in the control population. LVH was found to be common in the control population. The ECGs in the control population were taken almost 50 years ago, prior to the era of effective treatment of hypertension. This is probably the reason for high prevalence of LVH in control population.

Very little information is available about ECG abnormalities linked to exercise-related SCD in the general population. FinGesture study population with almost 4,000 SCD subjects is to our knowledge the largest study population of consecutive autopsy-verified victims of SCD in the general population. Our study setting and exclusion criteria offered a study population of 276 victims of SCD with a previously taken ECG. The total number of exercise-related deaths is quite small, which diminishes the ability to generalize our findings. The ECGs were taken on average around three years prior to the SCD; however, this time difference between ECG recording and the event is significantly shorter than in many prospective cohort studies. The control population was acquired from an older study, which may account for some of the differences observed between SCD patients and controls.

3.1 | Implications

In our study we found that fQRS complex in anterior leads was more common among exercise-related SCDs compared to SCD occurring at rest. This finding was especially distinct when a prior diagnosis of CAD was present emphasizing the potential role of anterior QRS fragmentation in exercise-induced SCD in CAD patients. These findings may offer new tools to identify patients with an increased risk to exercise-related SCD and for counseling the CAD patients who have such an ECG abnormality in the 12-lead ECG.

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REFERENCES

1. Stecker E, Reinier K, Marijon E, et al. Public health burden of sudden cardiac death in the United States. *Circ Arrhythm Electrophysiol*. 2014;7:212–217.
2. Niemeijer MN, van den Berg Marten E, Leening MJ, et al. Declining incidence of sudden cardiac death from 1990–2010 in a general middle-aged and elderly population: The Rotterdam study. *Heart Rhythm*. 2015;12:123–129.
3. Thompson PD, Franklin BA, Balady GJ, et al. Exercise and acute cardiovascular events placing the risks into perspective: A scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. *Circulation*. 2007;115:2358–2368.
4. Siscovick DS, Weiss NS, Fletcher RH, Lasky T. The incidence of primary cardiac arrest during vigorous exercise. *N Engl J Med*. 1984;311:874–877.
5. Albert CM, Mittleman MA, Chae CU, Lee I, Hennekens CH, Manson JE. Triggering of sudden death from cardiac causes by vigorous exertion. *N Engl J Med*. 2000;343:1355–1361.
6. Marijon E, Tafflet M, Celermajer DS, et al. Sports-related sudden death in the general population. *Circulation*. 2011;124:672–681.
7. Berdowski J, de Beus MF, Blom M, et al. Exercise-related out-of-hospital cardiac arrest in the general population: Incidence and prognosis. *Eur Heart J*. 2013;34:3616–3623.

8. Teodorescu C, Reinier K, Uy-Evanado A, Gunson K, Jui J, Chugh SS. Resting heart rate and risk of sudden cardiac death in the general population: Influence of left ventricular systolic dysfunction and heart rate-modulating drugs. *Heart Rhythm*. 2013;10:1153–1158.
9. Jouven X, Zureik M, Desnos M, Guerot C, Ducimetiere P. Resting heart rate as a predictive risk factor for sudden death in middle-aged men. *Cardiovasc Res*. 2001;50:373–378.
10. Teodorescu C, Reinier K, Uy-Evanado A, et al. Prolonged QRS duration on the resting ECG is associated with sudden death risk in coronary disease, independent of prolonged ventricular repolarization. *Heart Rhythm*. 2011;8:1562–1567.
11. Aro AL, Anttonen O, Tikkanen JT, et al. Intraventricular conduction delay in a standard 12-lead electrocardiogram as a predictor of mortality in the general population. *Circ Arrhythm Electrophysiol*. 2011;4:704–710.
12. Brenyo A, Pietrasik G, Barsheshet A, et al. QRS fragmentation and the risk of sudden cardiac death in MADIT II. *J Cardiovasc Electrophysiol*. 2012;23:1343–1348.
13. Das MK, Maskoun W, Shen C, et al. Fragmented QRS on twelve-lead electrocardiogram predicts arrhythmic events in patients with ischemic and nonischemic cardiomyopathy. *Heart Rhythm*. 2010;7:74–80.
14. Tikkanen JT, Anttonen O, Junttila MJ, et al. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med*. 2009;361:2529–2537.
15. Rosso R, Glikson E, Belhassen B, et al. Distinguishing "benign" from "malignant early repolarization": The value of the ST-segment morphology. *Heart Rhythm*. 2012;9:225–229.
16. Straus SM, Kors JA, De Bruin ML, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults. *J Am Coll Cardiol*. 2006;47:362–367.
17. Chugh SS, Reinier K, Singh T, et al. Determinants of prolonged QT interval and their contribution to sudden death risk in coronary artery disease: The Oregon sudden unexpected death study. *Circulation*. 2009;119:663–670.
18. Panikkath R, Reinier K, Uy-Evanado A, et al. Prolonged tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol*. 2011;4:441–447.
19. Aro AL, Anttonen O, Tikkanen JT, et al. Prevalence and prognostic significance of T-wave inversions in right precordial leads of a 12-lead electrocardiogram in the middle-aged subjects. *Circulation*. 2012;125:2572–2577.
20. Porthan K, Viitasalo M, Toivonen L, et al. Predictive value of electrocardiographic T-wave morphology parameters and T-wave peak to T-wave end interval for sudden cardiac death in the general population. *Circ Arrhythm Electrophysiol*. 2013;6:690–696.
21. Kaikkonen K, Kortelainen M, Eeva Linn, Huikuri HV. Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. *Circulation*. 2006;114:1462–1467.
22. Hookana E, Junttila MJ, Puurunen V, et al. Causes of nonischemic sudden cardiac death in the current era. *Heart Rhythm*. 2011;8:1570–1575.
23. Jette M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol*. 1990;13:555–565.
24. Reunanen A, Aromaa A, Pyorala K, Punsar K, Maatela J. The Social Insurance Institution's coronary heart disease study. *Acta Med Scand*. 1983;673:1–120.
25. Terho HK, Tikkanen JT, Junttila JM, et al. Prevalence and prognostic significance of fragmented QRS complex in middle-aged subjects with and without clinical or electrocardiographic evidence of cardiac disease. *Am J Cardiol*. 2014;114:141–147.
26. Das MK, Khan B, Jacob S, Kumar A, Mahenthiran J. Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. *Circulation*. 2006;113:2495–2501.
27. Das MK, Saha C, El Masry H, et al. Fragmented QRS on a 12-lead ECG: A predictor of mortality and cardiac events in patients with coronary artery disease. *Heart Rhythm*. 2007;4:1385–1392.
28. O'keefe JH, Patil HR, Lavie CJ, Magalski A, Vogel RA, McCullough PA. Potential adverse cardiovascular effects from excessive endurance exercise. *Mayo Clinic Proceedings*. 2012;87:587–595.
29. Torigoe K, Tamura A, Kawano Y, Shinozaki K, Kotoku M, Kadota J. The number of leads with fragmented QRS is independently associated with cardiac death or hospitalization for heart failure in patients with prior myocardial infarction. *J Cardiol*. 2012;59:36–41.
30. Toukola T, Hookana E, Junttila J, et al. Sudden cardiac death during physical exercise: Characteristics of victims and autopsy findings. *Ann Med*. 2015;47:263–268.
31. Morin DP, Oikarinen L, Viitasalo M, et al. QRS duration predicts sudden cardiac death in hypertensive patients undergoing intensive medical therapy: The LIFE study. *Eur Heart J*. 2009;30:2908–2914.
32. Zhang Y, Post WS, Blasco-Colmenares E, Dalal D, Tomaselli GF, Guallar E. Electrocardiographic QT interval and mortality: A meta-analysis. *Epidemiology*. 2011;22:660–670.
33. Watanabe N, Kobayashi Y, Tanno K, et al. Transmural dispersion of repolarization and ventricular tachyarrhythmias. *J Electrocardiol*. 2004;37:191–200.

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